are you going to alter the training technique that is listed in slide 102 to reduce complications when mere mortals try to do the surgery?

Slide 102 lists a number of objectives from training, most of which I believe are already, as I peripherally understand it, part of the ARTISAN training program. Can you tell me how you are going to change the training?

DR. STULTING: I'm not exactly sure that I understood the question. Could you repeat it?

DR. VAN METER: Yes, sir. On slide 70 you mentioned that proper training will reduce the incidence of complications. Slide 102 you list the training proposal but, as I understand it, this training proposal is pretty much how training has existed for ARTISAN investigators.

DR. STULTING: I don't think -- there is no question that this surgery is different from what ophthalmologists are used to performing as you could see from the video clip. There is bimanual dexterity that is involved. It's a little bit greater than the bimanual dexterity that we are used to having in other

procedures that we perform. That will have to be taught.

As a result of the clinical trials, there are techniques that we have learned that need to be taught perhaps differently, emphasized differently than were done in the clinical trial. We think that those will be possible to teach and that, I guess what you said was, mere mortals will be able to perform those techniques.

After all they do in the rest of the world outside the United States using the data that we showed you from Market Scope with implantation of phakic IOLs. This is the most common phakic IOL that is implanted outside of the United States where ordinary surgeons have a choice of intraocular lens implants to use and this is what they choose to use.

We think that the experience that we have had has made us better at picking out skills that we need to teach and in recognizing methodologies that can be taught to improve the performance and that's what we've learned from the clinical trials.

We would prevent all complications from

the lens? Probably not. We still see complications from cataract surgery and other procedures that we perform. I don't think technique will be any different but I think that the risks are well worth the benefit.

DR. VAN METER: Thank you.

DR. STULTING: May I pass the mike off to Dr. Thompson?

DR. THOMPSON: Just a quick comment. I consider myself a mere mortal and I get way more stressed out going into cataract surgery than I do going into doing ARTISAN. I have not found the training to be difficult. Approximately after five implants I had a nice comfort level so I do not think we are going to have a hard time getting ophthalmologists comfortable with this procedure.

DR. WEISS: Dr. Smith.

DR. SMITH: Janine Smith. I wanted to echo Dr. Bandeen-Roche's concerns regarding any data you might have on differences in the cases of patients that had gradable specular images for the endothelial cell counts.

I wonder if you have any data on the proportion of eyes that have gradable specular images in the 12 sites that had the Konan microscope? So that's one, the proportion. The second is could you identify any difference between the cases and people that had gradable images and the ones who didn't.

My concern is from my experience with that particular instrument which has issues that I'm sure we'll talk about later, it happens to be the corneas that have some abnormality that it is much more difficult to get good images in so you can understand why this might be an important question.

DR. STULTING: I appreciate the comment and made note of it and we'll try to address it. I can tell you from having looked personally at many of the images that were obtained during the first part of the study the problem with the images wasn't that there were very few cells, large cells, and unusual cells with Gute and other abnormalities. The problem was focusing, properly counting and whatnot. They were technical problems but I've made note of the question.

DR. WEISS: Dr. Huang.

DR. HUANG: I have some concerns about the safety and efficacy for this procedure in the low myope patient. As we all know, there are many refractive surgery options for the patient with low myopia nowadays. I'm just wondering that in the low myope patient with slightly shallow anterior chamber is the safety equity maintained and achieved in the efficacy of this procedure? Is it just as effective or as safe as some other existing procedures?

DR. STULTING: That's a good question and a good consideration. We looked at endothelial cell losses in patients who had more narrow anterior chamber than those who had deeper chambers and didn't find a correlation with that.

Having said that, I appreciate your concern. The sponsor believes that this is a technology that should be made available so that it can be used at the discretion of the well-trained and discriminating refractive surgeon.

With the information in hand and the proper training, that surgeon can make a reasonable

decision about what is the best technology to offer the patient. It's possible that a low myope may do better with an intraocular lens implant because of his corneal anatomy.

Perhaps it's someone who has questionable form fruste keratoconus and the surgeon doesn't want to take a chance on getting ectasia postoperatively. In that particular case the balance may fall toward an intraocular lens implant when for the routine patient with low myopia a corneal procedure may be most appropriate.

DR. WEISS: Thank you. We have one question from Dr. Macsai and we have one from Ms. Such and we'll do those two and then we'll conclude this portion.

Dr. Macsai.

DR. MACSAI: On the panel someone had asked about the endothelial cell counts in the patients that had their implant repositioned, etc. I was wondering if you could give us the endothelial cell data on the entire Group E because I did not have that to review prior to this meeting and I would like

to see the consistent cohort within Group E, the entire Group E. I think that is incredibly important because, as Dr. Van Meter stressed, we are mere mortals and what happened in that group is important.

DR. STULTING: I'll add my name to the list of mere mortal ordinary surgeons. To address your question, let me make note of that and see if we can get data for you when we come back.

DR. WEISS: Glenda.

MS. SUCH: Glenda Such here. Aside from thanking Dr. Weiss for bringing up the concern about what activities besides boxing and basketball or whatever a consumer might want to avoid doing, I believe during one of the discussions from the presenter we heard that nighttime activities that would be affected aside from having starbursts and halos during driving, one of the presenters actually had said the word newspaper print. I was wondering what other types of activities or type of events you've actually noticed being hindered by this lens with low illumination?

MR. McCARLEY: We haven't had any reports

as the sponsor from a site or from a patient that they have been hindered in a nighttime activity from having glare or halos or starbursts or any other visual effect.

MS. SUCH: Not during driving either?

MR. McCARLEY: That's correct. None that inhibit them from doing that.

DR. WEISS: One question in terms of the induced astigmatism, Doyle. You had mentioned that this was most likely from the wound. I assume corneal topographies were done to just confirm that anyone with astigmatism or maybe in some patients that, indeed, it was wound induced?

DR. STULTING: Corneal topography was not part of the protocol.

DR. WEISS: Okay. So it was sort of more the assumption or it went along with the refraction where the astigmatism was and where the wound was placed?

DR. STULTING: Right. We have refractions before and after and vector analyses to look at the astigmatic change from one to another.

DR. WEISS: And the astigmatic change would be consistent with the placement of the wound or did anyone -- is this just an assumption or did anyone actually look at it?

DR. STULTING: We didn't look at it probably in a sufficiently organized way to really address that.

DR. WEISS: Okay.

DR. STULTING: I think it was sort of believed that the investigators were sufficiently familiar with wound placement for cataract surgery that they understood what it would do.

DR. WEISS: Thank you. I want to thank the sponsor and we are now going to go on to the FDA presentation.

DR. TOY: Good morning, panel members. I'm Jeff Toy, the team leader for this PMA P030028, phakic IOL for the correction myopia. The sponsor has already given an excellent introduction of the results and a description of the device so I only have two slides to add.

This first slide is just to acknowledge

the PMA review team. They did a good job of expediting the review of this PMA. The team members are Don Calogero, Carol Clayton, Gerry Gray, Susan Gouge, Sue Jones, Bernard Lepri, T.C. Lu, Elizabeth Riegel, and Pam Reynolds.

Second slide is just the order of speakers for FDA presentation. Dr. Lepri will be first and giving summary of the clinical results and posing the question to the panel, and Dr. Gray will be second with the statistical analysis of the endothelial cell count. Thank you.

DR. WEISS: Thank you, Dr. Toy.

Dr. Lepri.

DR. LEPRI: Good morning, members of the panel, FDA colleagues and guests. In my presentation this morning I will just present to you some highlights that you will need for consideration for making your recommendations today.

This panel has specific goals to achieve today and those will be for us to assess, evaluate, and identify. We'll be assessing the risks and benefits and evaluating the effectiveness and safety

outcomes presented by the sponsor and the PMA and their presentation here today.

Some of the risks that we've identified are operative and postoperative. Operative risks may include improper enclavation leading to surgical repositioning, wound leakage, infection, induced cataract and/or corneal damage due to surgical trauma.

Postoperatively one may see elevation of IOP inflammatory responses, the potential for pigmentary glaucoma as a result of iris irritation, critical losses of corneal endothelial cells and function, retinal detachment and dismemberment of the IOL itself with concomitant optical side effects such as glare and halos, etc.

Correction of high refractive errors without the optical limitations imposed by spectacles and the complications of long-term wear contact lenses is perhaps the major benefit for the patient, while reversibility and expanded options for treatment of high-refractive errors benefit both the practitioner and the patient.

I'm going to give you a capsule view of

the effectiveness and safety outcomes that were presented here today. Under effectiveness some major highlights are UCVA, BSCVA, predictability of RSE, and the stability of the MRSE.

Uncorrected visual acuity of 20/20 or better was achieved by more than 30 percent of the overall treated subject population at one, two, and three years. UCVA of 20/40 or better were achieved by greater proportions ranging from 84 percent up to 87 percent over the three-year period reported in the study.

As one would expect, BSCVA shows that at least 79 percent have 20/20 or better and essentially 100 percent had BSCVA of 20/40 or better in the overall treated population. The ARTISAN showed a high degree of predictability in targeting refractive correction. At least 72 percent were within a half diopter of intended correction and 94 percent and higher were within 1 diopter.

At present refractor procedure stability is determined by evaluating the proportion of eyes that show variability in refraction no greater than 1

diopter between consecutive visits and refractions at least three months apart and mean differences of less than .5 diopter over a yearly interval.

The ARTISAN study population showed 95 to 98 percent were within 1 diopter of refractive change between consecutive refractions and mean differences in refraction ranged only from -.02 to -.05.

Safety issues where the BSCVA, which was already discussed, induced astigmatism, cells and flare, corneal edema, increased IOP or glaucoma, cataracts, and endothelial cell loss and corneal compromise.

Induced astigmatism of 2 diopters or more was reported in proportions ranging from two percent to 3.5 percent and the established target for refractive procedures has been set for less than 5 percent. The rates of inflammatory responses postoperatively were in the expected ranges that one would expect for this type of surgery.

While there were several reports of elevated IOP none persisted beyond 20 days post-op and were secondary to either postoperative steroid

treatment or a few cases of incompletely aspirated viscoelastic. The cases that require short-term treatment all responded adequately.

While there were 49 lens opacities reported in the study only four were visually and clinically significant. The others were due to careful observations on the part of the investigators identifying normal age related chances in the crystalline lens. And of the visually significant cataracts three required extraction and the fourth one resulted in a loss of two lines of BSCVA but, to the best of my knowledge, was not worse than 20/40.

While there were no cases of actual corneal compromise reported during the investigation, endothelial cell loss changes were reported during both the short term in the domestic study and in the scant but long-term data from the European study. Dr. Gray will present the detailed analysis of these changes following my presentation.

I'm going to ask you to identify thresholds of critical inclusion criteria to minimize risks and perhaps the population it may benefit most.

With considerations for the outcomes presented to you by the sponsor here today and in the PMA, the panel will be asked to make these recommendations regarding patient selection criteria, the risk benefit ratio of this device, and its associated surgical procedure and to establish criteria for product labeling if approved for marketing.

The use of phakic IOLs for the correction of refractive errors shows concern for the long-term effects upon the integrity of the corneal endothelium. The entry criterion established by this sponsor at the inception of this study was a minimum pre-op cell count of greater than or equal to 2,000 cells.

On the next slide and on slide 32 I need to make a correction. The mean pre-op starting is 2,754 and not 2,500 as on the copy of the slides that you have in front of you.

The sponsor's response to FDA's challenge of endothelial cell change data outcomes resulted in the sponsor's development of the charts you see presented here in this slide. Assuming a baseline cell count of 2,754 cells and assuming linear loss

over time, the sponsor shows that after 30 years the cell count may drop to 1,272 cell per millimeter-squared. Of course, it is important for us to keep in mind the large margin of error viewed by spectral microscopy and the mathematical assumption of linearity and cell changes over time in these calculations.

The very nature of endothelial cell examination and change is affected by many variables. One variable identified in this study was anterior chamber depth. While the same size was low, it is particularly relevant to the ARTISAN lens its position in the anterior chamber and one can see from the six-month post-op period to three years for the seven eyes having anterior chambers ranging from 3.0 to 3.2 mm that there was an estimated cell loss of 8.99 percent.

The ARTISAN also offers two models whose optic sizes vary. They are 5 mm and 6 mm and relate to the patient's pupil sizes. The relevance of these optic sizes is related to performance in low-light environments and the potential for symptoms and complaints of glare and halos that may impact

functioning such as in nighttime driving. The sponsor presented the outcomes of patient satisfaction by questionnaire responses for our consideration.

The implied refractive benefits of the ARTISAN have already been discussed here today and are directly related to the targeted refractive range. You will recall that only a small percentage of eyes were treated below -8 diopters of myopia.

I am not going to present the questions now. We will present the actual questions to you following Dr. Gray's presentation of the endothelial cell data. Thank you.

DR. WEISS: Thank you, Dr. Lepri.

DR. GRAY: Good morning. My name is Gerry Gray and I'm going to discuss the results from the endothelial cell counts in this study. I'm the team leader for the Cardiovascular and Ophthalmic Statistics Team. This submission was mainly reviewed by a member of our team, T. C. Lu.

Just a synopsis of what we're going to be talking about here. The purpose of the endothelial cell count is to investigate the effects of the device

on the endothelial cells through time. We have endothelial cell counts and measurements from specular microscope photographs. There are multiple images for eye after all 2,000. We have counts at baseline six months one, two, and three years.

As you've already heard in some detail from the sponsor, there was a very large variability in the initial set of data and so images were reread as possible and the net result is we have 353 available eyes from reliable machines that were recounted in one reading center. That was a total of 1,144 actual observations eyes by visit. As a statistician I need to point out that we don't have any control group here so it's very difficult to evaluate the results without an actual control.

So there is no control and the question is what do we compare these results to? We want reasonable assurance that the endothelial cell density is preserved. The normal loss due to aging is apparently around 0.6 percent per year. The point for concern appears to be around 1,000 to 1,200 cells per millimeter-squared.

There are several sources of guidance or preliminary guidance and they are all written in terms of trying to place an upper confidence limit on this rate of loss. The FDA draft guidance and the discussion from this panel several years ago set an annual rate from three months to three years, an upper 90 percent confidence limit of 1.5 percent.

The ISO and ANSI documents are not actually, I don't think, written in terms of standards for acceptable rate of loss but those both suggest you calculate a sample size for this kind of study using a 2.0 upper 90 percent confidence interval.

Here is a visual representation of the data that we do have from a recount study. Each vertical bar is one of the visit, base line six months, one, two, and three years. The green indicates that we have actually a count in that time and the white indicates we don't.

Individual eyes can be read horizontally across here. Here on the bottom are the 57 eyes that were measured at all time points. There were 126 extra eyes that had a baseline measurement and by the

end there is actually 50 of them left here so there's 107 eyes that have both base line and three-year measurements.

Then there's a fairly large portion of eyes, 170 right here that have no baseline measurement. Then you can see these numbers indicate the number of people that started in at those various points in time.

A couple of comments on this graph. This is not the normal pattern. We are used to dealing with

-- this is not the normal pattern of missing we see where initially everyone has a baseline and people drop out through time.

This is somewhat unusual because we have this very large group that actually doesn't have measurements at the beginning. That was, I'm pretty sure, due to the fact that the study was sort of given a lot more importance part way through. Initially we don't have baseline measurements for these people.

Another comment that I want to make that came from the discussion, the earlier questions, the

question of is there a bias problem because perhaps some of the measurements are thrown out because they were low. The question is how is that going to change the rate of loss through time if there's a bias?

What I want to point out is that if there's a bias, there's more people missing here at the beginning than there are at the end so I'm not sure if there's a bias how it would affect any kind of results we have here today. I think that's an unanswerable question.

This is a plot of the actual data that we do have, the 1,140 observations from 353 eyes and the blue line just connects the means at each time point. The red line across the bottom, just for your reference, is 1,200 cells per millimeter-squared.

Now, what we're interested in is the steady state, if you want to call it that, the long-term loss that we can expect to see. That estimate depends on a lot of things. It depends on the model that we use, whether we account for an initial operative loss or not so the function of formal use, whether we use the baseline in the end or some form of

regression, the cohort we use, the details of the statistics.

As an aside, it's not entirely clear to me that natural loss for untreated patients is actually steady state either. That further complicates any kind of extrapolation you want to make.

All that aside, there's really not that much variability in the estimates of long-term loss from these data. The sponsor presented an annual loss of 1.7 percent based on 183 eyes but had a baseline count. That calculation is based on a regression that includes the baseline. A 90 percent confidence interval for that is 1.3 to 2.1 percent.

An alternative that I think might be slightly better uses all the data that we do have and tried to account for the missing using something called multiple imputation. That actually gives a fairly similar result, 1.8 percent annual loss, 90 percent confidence interval 1.3, 82.2 percent. Both of these estimates account for correlation within patient in a reasonable way.

Here are the results from the best, the

1.8 percent loss per year. If you actually pull out the other one on top of this, the lines are virtually superimposed. It looks almost the same, 1,200 cells per millimeter still there as a reference.

Now, of course, this is what we have so far for three years and what you really are concerned about is what happens in 10, 20, 30, or 40 years so we want to do some extrapolation if we can. Before we do that, it's my duty to remind you that we are trying to -- it's always a questionable exercise to extrapolate and we are trying to extrapolate 10 times the range of the data that we do have.

All that being said, though, probably some type of -- you have to make some extrapolation to make a judgment, either formally or informally. If we do it formally, it's very dependent on the model we use and the assumptions we want to make, is it linear, exponential, whatever kind of decay.

The problem is with only three years of data we can't really distinguish between these models. There's no way of telling what happens if things change in 10 years. Because of that I think you also

should really consider if it's necessary to obtain good long-term data and how you might want to go about that.

One more thing. We do have some additional long-term information that has been referenced previously. The sponsor has provided additional four-year data on 27 patients who showed a 1.63 percent loss between three and four years. Then there is some additional long-term information from a 19-patient European cohort.

Basically the same follow-up is in this study but there is an additional point t 10 years. For those patients their mean counts went from 2,666 to 2,180 at 10 years. That's an 18.1 percent decrease over the 10-year period. Six percent of that was in the first six months.

That translates into annual rates that you see down here at the bottom, 1.2 overall. The rate between six months and three years was actually fairly high, 2.9 percent, and the rate between three years and 10 years is actually fairly low, 0.7 percent. You can make what you will of that.

After we got all the caveats and other data aside, here is a picture of the linear extrapolation that you would produce using the 1.8 percent loss per year. On the graph are also confidence limits, the dash lines of the confidence limits on the regression and the dotted lines are the confidence limits for predicting an individual.

You can see there is a fair amount of variability and what really matters is right from here there is a fair amount of variability in this direction. In other words, the variability and the time the person might take to reach 1,200 cells per millimeter-squared. All this, of course, still assumes that whatever happened in the first three years is going to continue linearly for the next 37.

Using a linear model we can actually -- and using the rates of loss that we get based on the estimates we produce we can produce a table that shows the years until predicted 1,200 cells per millimeter-squared. You can see of you start out at 2,000 cells then after 12 to 17 years, depending on how cautious you want to be. you are going to be at around 1,200.

If you start out with 3,200 cells, then you have maybe 30 or 40 years until you reach 1,200. Again, this all should be taken with a grain of salt because it's an extrapolation and there is a fair amount of error.

Maybe a little more important than the average cell loss through time is a question of how are the individual patients faring here. In other words, what proportion of the patients are going to show a cell loss that's greater than some critical amount. Another way to ask that is what proportion of patients are going to have cell densities less than 1,000 to 1,200 in 10, 20, or 30 years.

Again, it's hard to answer with much confidence because now we're not just extrapolating the mean. We are trying to extrapolate the percentiles. We want to know what's the lower 10 percent of the patients and where are they going to be in 10 years.

The best I can think of with the data we have is to take all the patients that we actually have. We can actually fit a regression. We have more

than two observations on them, more than two follow-up visits. We can fit a model that actually gives each of them the possibility of having their individual rate of loss.

The model actually is called random effects regression. What it does is assumes that the losses come from some normal distribution so the rates of loss are coming from a common distribution. That's what you see here. These are the results. The dark lines indicate the 1.5 and 2.0 percent losses. You can see that most of them are below 1.5.

So also using that same histogram we can save the percentage of patients with annual losses worse than a particular amount what can we expect. Using these data and this model you can say that probably 5 percent of the patients are going to have losses of 2.2 percent or more, 99 percent of 1.5 percent or more.

Again, I need to give some comments on these estimates because they are fairly highly dependent on the model used to arrive at the individual patient estimates. The model, on the one

hand, reduces the variability because it shrinks the estimates. The estimates for each patient are moved toward the overall mean so that reduces the variability and that would tend to make this number a little bit smaller.

On the other hand, the annual loss in this model where I didn't do the imputation was a little bit higher so that would tend to counteract that to some degree. This is the most I can give you right now.

Just to summarize, if I can, in one slide, the estimated annual loss is apparently about 1.8 percent per year with a 90 percent confidence interval 1.3 to 2.2. For individual patients maybe a third of them have annual rates of loss more than two and five percent have rates of loss more than 2.2. Again, it is necessary to do some form of long-term extrapolation but you need to try to interpret that with whatever amount of caution you want to put into it. Thank you.

DR. LEPRI: Okay. I'm going to present question 1 to you and then there are several slides of

background data that you need for consideration. You have the copies in front of you. I'm able to put all of those charts into a slide form so you may want to refer back and forth to them.

The first question is:

1. Do the endothelial cell data presented above by overall analysis, stratified by anterior chamber depth and the extrapolations over time provide reasonable assurance of safety of the ARTISAN myopia lens?

Here is the data that was presented and the hardcopy questions that you have in front of you. The first slide shows the estimated changes in cell loss at six months, one year, two years, and three years. The standard deviations, errors, and confidence limits.

The next piece of information that you are to use is the percent change from baseline. It shows also for the intervals of six months through three years. The percent change by period, the difference between six months to one year, one year and two years.

In this slide it shows that in a paired analysis the percent change calculated between baseline and three years post-op was -4.76 percent with a standard deviation of 7.8 percent. When analyzed by interval one can see that losses appear to be higher between the second and third postoperative years.

The sponsor did show that when they eliminated the one site, that all had the specular microscopy done with the same device, when they had changed employees midstream during the study when they removed that data out, that dropped from -2.37 percent to minus 1.68 percent.

DR. WEISS: I would just request whoever has the cell phone if they could silence it forever. Thank you.

DR. LEPRI: The next slide shows the endothelial cell count change over time from baseline stratified by anterior chamber depth for the 3.0 to 3.2 mm anterior chamber depth. You can see the changes over time. Even though the ends are small, there is no statistical significance to this but we

want it for consideration for potential trend.

The next slide is endothelial cell count changes from six months to three years stratified by all of the anterior chamber depths in the study. The last slide is the subjects with three and four-year follow-up having that mean ECC at pre-op of 2754 with an end of 27 to show what their changes were from three to four years.

2. Do the other data presented in the PMA outside other endothelial cell data provide reasonable assurance of safety? Those are to be considered as two separate issues.

This is the background for Question 3. The proposed statement of indication reads: "The reduction or elimination of myopia in adults with myopia ranging from greater than -5 to less than -20D with less than 2D of astigmatism at the spectacle plane; Patients with documented stability of refraction for the prior six months, as demonstrated by a spherical equivalent change of less than or equal to 0.50D."

3(a). Does the panel recommend any

modifications to the proposed statement of indications with respect to:

a). minimum anterior chamber depth;

b). maximum pupil size (the 2 models of the ARTISAN are intended for patients with pupil sizes up to 5.0 mm and up to 6.0 mm; and

c). minimum preoperative endothelial cell density? The outcomes of ECC changes reported in the background data for question No. 1 above should be referenced if the panel wishes to recommend an acceptable minimum endothelial cell density to quality a patient.

4. Do the panel members have any additional labeling recommendations?

DR. WEISS: Thank you very much. We are actually doing fairly well on time so what I would ask is if the -- I hear chuckles. I guess usually we haven't been in the recent past. What we're going to do is if the FDA could perhaps entertain some questions before lunch and I'm going to ask if anyone from the panel has any questions.

DR. BRADLEY: I have a quick question for

Dr. Gray.

DR. WEISS: By the way, I wanted to thank Dr. Gray for that wonderful first slide showing where people fell out in terms of participating and not participating in specular microscopy because that really just clarified things amazingly.

DR. BRADLEY: Dr. Gray has presented a similar presentation some time ago, if I recall, to this group. In both presentations you have admonished us to be very aware of the shortcomings of extrapolation. In spite of that, we go ahead and extrapolate primarily because most of us are not very sophisticated. I think you always give us a linear model which we can sort of understand because we can all draw a straight line with a rule.

But in the end, from my perspective as a scientist not involved in this field, I just find myself incredibly uncomfortable with this extrapolation and I wondered do you know of any data from some other product, other condition that indicates that the pattern of cell loss seen in the first three years is, in fact, continued on in a

linear way over five, 10, 15, or whatever years? I don't know this field at all and maybe you could help.

DR. GRAY: Well, first of all, you might have noticed that I said in this presentation that some amount of extrapolation is necessary to make a decision. Even though it's my job to warn you about it, you still have to do it.

In terms of further data that might corroborate any kind of model, all that I know about is what we presented in the 19-patient European cohort. I actually, if you really want to see it, I have a plot somewhere. If you plot those 19 patients superimposed on the extrapolation, they basically cover the whole range of error for prediction of an individual. They are right there. There's only 19 of them and when you look at that they have a fairly large amount of variability so it doesn't really help us to decide sort of a relatively subtle difference between something like a linear loss or an explanational loss or something like that.

DR. BRADLEY: Thank you. I'll open the question up to anybody else in the room who is

knowledgeable in the issue of endothelial cell count data. Are there any data for some other product, some other disease that we have long-term data on?

DR. WEISS: Dr. Grimmett.

DR. GRIMMETT: Dr. Michael Grimmett. In my review of endothelial data for this panel perhaps a year ago, the only other data that I could find would be Bill Bourne's data. His data had several limitations in that the patients that had the cataract surgery had a wide variety of the types of procedure whether it be extracap or intracap.

Specular microscopy images were not standardized. I don't believe that the Konan machine was around at that time. I didn't go back through the data to look at it year by year to answer your question did the first three years actually predict what happened 10 years later. That's the question you're asking. But his data was such small numbers and such a wide variety of procedures that I'm not sure that would actually even looking at his data would actually answer it. From my review I'm not aware of another product where we have the answer to

that question.

DR. GRAY: Here is the trial I was referring to where the red dots have the 10-year European data. You can see they neither confirm nor deny anything about -- their variability is fairly large here in these 19 patients and so they don't really tell me that the model is terribly wrong but they don't help me distinguish between fairly subtle differences.

DR. WEISS: Dr. Huang and then Dr. McMahon.

DR. HUANG: I know we spend a lot of time on endothelial cell counts from the FDA as well as the panel reviewers as well as the sponsor. I would like to look at this problem with a little bit slightly different angle. Truthfully that the cornea function is not really predicated on the absolute number of the endothelial cells.

It's really their functions. So are we looking at the cells as indicative of function or should we just look at the cornea thickness as a function to see if the cornea retains integrity

because clinically we have seen many patients with endothelial dystrophy with reduced cell count but over the years they don't have any cornea decompensation.

Even though the cell number continues to decrease, that doesn't mean the cornea is decompensating. That is my concern about all these number calculations. I understand that we need to have safety guidelines but, on the other hand, that's the only safety guideline that we need to be concerned about cornea integrity. Thank you.

DR. WEISS: I think the difficulty will be that the cell count is going to be much more sensitive, perhaps not totally significant, than the corneal thickness because as we all know as corneal surgeons, the thickness or the cornea will decompensate at a much lower cell rate.

If you are a 20-year-old patient and let's say you're losing your cells at 3 percent per year, and it's linear and continual, then we would obviously have concerns at some point. You may get into the risk of having decreased corneal function. These are all very difficult questions because I think what

we're being told by FDA and by sponsor we have a 1.7 to 1.8 percent corneal endothelial cell rate loss in the first three years.

It doesn't stabilize. What we all know is the only time this will become significant is many, many years down the line past when hopefully all of us will be retired at that point and not meeting at this panel meeting but we need to project into the future with data that we don't have.

Dr. McMahon.

DR. McMAHON: This goes back to Dr. Gray. This might be extraspeculative but in that European data is it possible to use a nonlinear model? The issue here is there a decrease in the rate of change at the end that would show some flattening? I mean, the plots that you show demonstrate that these individuals if this is real are doomed if they live long enough.

DR. GRAY: It's possible to fit a nonlinear model but it's impossible with the data we have to distinguish between a linear or a nonlinear model. We can do those fits if you want to

extrapolate in some other way with some other model, you can either make it curve one way or the other and look either better or worse. I have no basis based on the data we have to pick one of those models over the other.

What I present here is just the straight line middle-of-the-road linear extrapolation. If you have some reason to choose otherwise, we can entertain another model. It's difficult. It's impossible with the data we have, I think, to distinguish between those.

DR. WEISS: Any other questions from panel?

DR. BRADLEY: Sorry, Dr. Gray. You stepped down. I'm still not clear on what you've shown us here. The red dots --

DR. GRAY: Is this on?

DR. BRADLEY: Let me get my question out and you can answer it. For example, these are 10-year follow-up. Presumably these people at this time are 10 years older and one wonders what the age match norms might be for this group. That looks to me like

most definitely the means must be lower in this sample that you put up there, the 10-year follow-up.

I wonder how different are they to age-matched controls, age-matched norms, for that group of people whatever age they were. I'm trying to get a sense does this group really have lower than normal looking endothelial counts. That wasn't a very clear question. Sorry about that.

DR. GRAY: Well, first of all, let me make it clear that I did not do -- these red points were not included in making this fit at all because I didn't -- I don't have enough information to have any idea whether we can pull together the data and use them in the same model or not. This plot was only made just in case we wanted to see how it looked instead of looking at the figures that I presented in slide No. 10.

Again, all I had, I personally got these data last week so I didn't have a lot of time to fiddle with them. All I had was the -- I don't have the co-variates. I don't know their ages. I don't know anything about them. I don't know the pupil

diameter, none of that stuff. All I know is -- all I got was the counts at baseline and the various follow-ups.

In the 10-year European, the slide that had that was just to indicate it. This is all we really know about long-term. This is the best we have in terms of long-term follow-up. This plot is just another way to look at that to see if there was some obvious red flag that any kind of extrapolation was off the mark. Really what the plot tells you is that there's not much information here.

DR. WEISS: Dr. Mathers.

DR. MATHERS: Bill Mathers. What you're saying is that those red dots are actually extraneous to this graph. They happen to fall right down the middle where the extrapolation is which would mean that the extrapolation seems to be consistent with the 10-year data of the European but, of course, you can't really say that.

DR. GRAY: I would say it's not inconsistent.

DR. MATHERS: It's not inconsistent.

DR. GRAY: I'm a statistician. But also there are some patterns in the European data that are different than the data we see here. For example, 353-eye cohort that we looked at there was virtually no change between baseline and the six-month follow-up which is counter to anything I have been led to expect.

Whereas for this European cohort there was a six percent loss between baseline and six months. So the patterns even though it comes out the same in the end at the 10-year point. The patterns up here at the beginning are somewhat different. Who knows if it's just due to the few number of patients or that they are really different patients. The population is somehow different demographically. I don't have that information.

DR. MATHERS: But to the subjective eye it looks like those red dots were used to calculate it because they look smack on.

DR. GRAY: They do but you will also remember that I mentioned I think it's three or four of them above the 90 percent line and four or five of

them are below. They actually have a fairly large amount of variability compared to the line that we do have.

I don't know how they got these counts. I don't know how the counts were standardized or anything but the amount of variability is actually fairly large here compared to what we had seen before in the current data set.

DR. WEISS: Is there a zero timeline for the European data? We have it on the 10-year.

DR. GRAY: If you look at slide 10 at baseline, there was 2,666 which was 100 cells lower than the mean and about 100 cells lower than the 2,760 in the current cohort so they started out slightly lower.

DR. WEISS: So just following up with what Dr. Mathers is asking, if that was plotted out there, would that fall quite similarly with the black line?

DR. GRAY: If you look at --

DR. WEISS: That would sort of correlate with what Bill is asking, that if it looks similar at zero and it looks similar at 10, then maybe it

actually --

DR. GRAY: The change --

DR. WEISS: Maybe it's not inconsistent with being similar.

DR. GRAY: Actually, the change for the -- I didn't want to make too much of -- we only have 19 patients and I don't know much about them but, having said that, for that cohort the average loss between six months and 10 years, the annual rate is 1.2 percent. It's actually lower than what we saw in the PMA cohort.

They had a very large drop at the beginning and then they leveled out somewhat. If you look at slide No. 10 it has a whole bunch of different ways of looking at the data to try to help you make some sense of that.

DR. WEISS: In the European data they only had 19 patients and there was a large amount of variability so all of these are deficits of over analyzing this data. Having said that, they have a 1.2 percent cell loss rate. Okay, good. From six months to 10 years.

DR. GRAY: They had a fairly high rate of loss between six months and three years, 2.9 percent. It was high. And then between the two time points, three years and 10 years, it dropped off to 0.7 percent. If you are optimistic you say the long-term rate is close to normal. If you are pessimistic you say the initial rate in the first three years was quite high and I don't really believe -- there's not enough data here to really tell what is going on so it's a judgment at this point with those 19 patients in my opinion.

DR. WEISS: Dr. Macsai.

DR. MACSAI: Dr. Gray, can you address something about this slide? I thought enrollment criteria was 2,000 cells or above. On the slide at the zero there's a whole bunch of little points. Maybe it's my refraction. I can't see how many little points but they are below 2,000.

DR. WEISS: You need to get an ARTISAN.

DR. MACSAI: My contrast, I think.

DR. WEISS: Sorry. Getting close to lunch.

DR. MACSAI: It seems like there are little dots on your graph below 2,000 at baseline.

DR. GRAY: There are.

DR. MACSAI: How is that possible?

DR. GRAY: Well, it looks to me like there's four or five dots below baseline at 2,000. You will recall that these are the recount data. These are not the initial counts so it could have been that when the patient was enrolled whoever did the endothelial cell count deciding it counted them one way, and you will remember there is a fairly large variability in the counting process so it's not surprising that a few of them actually came out lower when you recounted them. That's why the new suggestion is three photographs per person and standardization of the counting procedure to try to minimize that kind of variability.

DR. MACSAI: So we're not even 100 percent certain that our baseline counts, because these are based on one picture where all of those below 70 were kind of thrown out and we don't even know if that amount was thrown out was randomly distributed or

skewed in some way. We don't even know if our baseline is right is what you're saying in a statistical manner. I mean, where you don't want to be committal but that's what it sounds like.

DR. GRAY: What I'm saying is the sponsor had a slide that talked about the about of variability in the measurement of the endothelial cell density. There actually is inherent in this whole process a fair amount of variability. We take photographs of some location in your eye that can vary. Some of the photographs turn out good or bad for whatever reason and then we have people trying to count and to obtain a density, a cell density.

Just that whole process has a fair amount of variability in it. When you say sure, we're not positive of any of these counts. They have some measuring error. The recount data have less variability than the original study.

DR. MACSAI: Based on what do you say that? I mean, there's no standardization. It sounds like there's no check and balance done before it started.

DR. ROSENTHAL: Can I just explain something?

DR. MACSAI: Yeah. I'm really confused.

DR. ROSENTHAL: Their initial endothelial cell counts were done with large -- were not done in the standardized way. They were all over the board when it came to the variability. The Agency asked them to go back and to try out of this large number of eyes to get those that were taken standardly, were counted standardly, and were evaluated standardly. It's the best, frankly, I think we can do particularly when a new modality to look at the endothelial cell counts came up in the middle of their study.

DR. WEISS: Dr. Schein. Sorry.

DR. ROSENTHAL: They were all using different methods of doing it.

DR. WEISS: Dr. Macsai wanted to follow up and then Dr. Schein and then Dr. Grimmett.

DR. MACSAI: I feel an obligation here to make a follow-up statement, Dr. Rosenthal.

DR. ROSENTHAL: Sure.

DR. MACSAI: I believe that the Konan

specular microscope was available in 1997. Whether or not someone chose to utilize it it existed. Let's not preclude that it came about in 1999. That's point No. 1.

Point No. 2, from our history as ophthalmologists knowing the complications of anterior chamber intraocular lenses in patients, the Lysky, the ORC, when we designed these studies using an ACIOL I think it behooves the sponsor and the Agency to address these critical issues at the beginning before we move forward with implantation in patients because now we're looking at maybes.

DR. WEISS: Dr. Rosenthal.

DR. ROSENTHAL: I have to stick up for the Agency a little bit. I think in 1997 there was not as great a science of endothelial cell count as there is in the past three or four years. Certainly working on it in the standards group it was a very contentious issue and it took a long time to come to some conclusion how best to do it.

I don't know if Donna wants to comment on that. When a company puts together a protocol for an

IDE, we have to use what is currently considered the best science. Frankly, the science of endothelial cell counts in 1997 did not have a quality standard.

DR. WEISS: That will be the last word on that subject. I would like to go back to questioning. We just have a few minutes right now. Dr. Schein, if you have anything that you -- a question as opposed to any comments.

DR. SCHEIN: You've taken a comment right out of my mouth but I have one last question for Dr. Gray. Putting the cornea aside for the moment, I'm interested to know if you did any time dependent analyses of other complications, development of lens opacities, need for cataract surgery, intraocular lens or lens exchange, retinal detachment, etc., etc., both within the time frames of the data that you have and an extrapolation into the future.

DR. GRAY: The brief answer to that is no, I didn't do any of those analyses.

DR. SCHEIN: I would suggest they might be useful if for nothing else than patient education to describe whether if you survive the first month or

year or 18 months, that the complication rate goes down dramatically or the converse obviously equally important.

DR. WEISS: Fifty seconds.

DR. BRADLEY: Dr. Bradley. Again, Dr. Gray, question from your analysis. Did you notice whether the cell-loss rates correlated with the initial cell count.

DR. GRAY: As far as I could tell they did not. There was no significant indication that the rate of loss was a function of the baseline count.

DR. BRADLEY: So would the appropriate interpretation of that result be those with the low initial cell counts are at the greatest risk?

DR. GRAY: Yeah, I would say that's a fair interpretation of that.

DR. WEISS: Depending on how long --

DR. GRAY: As far as I recall, there was not -- it's difficult to work with the data when a lot is missing like this but I couldn't find any association between the baseline count and the rate. As far as I can tell the best thing to do is just

assume that it isn't a function of the rate and if you are low to begin with, you're at a higher risk.

DR. WEISS: Thank you very much. 12:30. We'll break for lunch for one hour.

(Whereupon, at 12:29 p.m. off the record until 1:36 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:36 p.m.

DR. WEISS: Okay. So what I would like to do before we go to -- we are going to be starting -- before we start committee deliberations, I had one question for the FDA which was on the basis of their presentation if they any recommendations as far as a time point after lens implantation, which would make it much easier to extrapolate, the endothelial cell count some years down the line as opposed to having to wait 20 years to find out what the answer would be in 20 years. I don't know who would be able to answer that one for us.

DR. GRAY: I can give you my opinion on that.

DR. WEISS: That's the one we want.

DR. GRAY: What you're trying to do is extrapolate 10 times the range of the data that you have. That makes any kind of distinguishing between -- several models could probably fit equally well within the relatively short amount of time you have, three, even if we have four years, and still be fairly

divergent after 30 or 40 more years.

It's going to be very difficult in terms of extrapolating out 40 years and know anything until we do get to the 10 or 20-year point. That's obviously somewhat impractical in terms of making a decision about approval.

Every year helps. Every year that you have further on that has no obvious increase and perhaps a decrease the better off you are. You are never going to be able to prior to approval have enough data to definitively say that it's one particular kind of functional form as far out as you want to go.endothelial

DR. WEISS: So from what I understand you to say that if we have four-year data or five-year data, that would not make the answer anymore clear than having three-year data.

DR. GRAY: In terms of the extrapolation I don't know that it would make that much difference in terms of distinguishing between a straight line and a curve, something like that.

DR. WEISS: Okay. Thank you.

There were a few questions that we had asked sponsor to look up. I'm told they have the answers to some of these. If they could come forward. There was a question I had about pupil size and explantation and a question that Dr. Casey had and Dr. Smith had.

DR. STULTING: Thank you, Dr. Weiss. We worked on this during the lunch break and I'll share with you the data that I have. There may be some more available later in the day. One of the questions that I may note of was the issue of mesopic pupil size and lens optic size. The sponsor did a multi-variate analysis looking at the presence of visual symptoms at night looking for correlations.

One of the correlations that they sought was mesopic pupil size greater than the lens optic size. In the cohort there were 56 first eyes enrolled and 31 who answered the questionnaire who fit this criterion. There was no correlation found in that analysis. I don't have power calculations available. That is something we can get for you later.

The second question that I made note of

was some concern about the possibility of bias in the selection of recount patients. I want to spend just a minute going over the protocol that was used to select those eyes.

The selection of sites for the recount was based only on the availability of instrumentation. It is possible that there is some unrecognized bias that people who are particularly good surgeons happen to have particularly good specular microscopes or something like that that we can't definitively and absolutely rule out, but there was no intent for that.

All available readable images regardless of endothelial cell morphology were included. In fact, this was a masked selection. The images were read -- were obtained and read at a central center not knowing who they belonged to, whether they were preoperative or postoperative, etc.

Once they were read, then a minimum of two readable images at different time points was required in order for an individual to be a member of the recount study. The other question that was related that was asked was how many images with only a few

cells were eliminated? The answer to that is there were 12 poor quality images eliminated because there were less than 70 analyzable cells in those images.

Those were the exclusions among 1,156 images that were analyzed leaving a total of 1,144 images which formed the data set that the recounts were derived from. We believe that the elimination of these few images probably didn't have anything to do with the results.

The third question was endothelial cell counts for Group E. Remember Group E was the group with replacement intraocular lenses, previous corneal transplants, custom made lenses that were fabricated with powers outside of the usual range, best corrected acuities less than 20/40.

Nine of these were included in the recount analysis. Three of them had replacement intraocular lenses. Two of them had custom lenses. Four of them had best corrected acuity of less than 20/40. There were 23 observations in this group so it was a relatively small group and in these there was an average loss of 2.67 percent per year. Recognize that

one-third of these were people who had had an extra surgical procedure to remove the intraocular lens.

A question was asked about endothelial cell count reliability. I answered it by saying that the protocol did not have any internal controls for reproducability. However, I would like to share with you some data about endothelial cell count reliability since the question was asked.

Once the images had been obtained, screened and read at a single trained central center, those images -- 50 of those images were randomly selected and sent to another reading center. This is a center that was outside of the investigational sites and a center that most of you would probably recognize that normally does endothelial cell counts.

So these same images were read by the second center. This then is a test of reproducability of reading alone because they were exactly the same images. The differences un the mean cell counts in this exercise was 0.8 percent, not significantly different from zero. But the standard deviation was relatively large, 24 percent, ranging from -47.2 to

+48.8 percent and 28 percent of these readings showed a more than 10 percent loss or gain. So this speaks to the ability to read these images. I speaks to the reliability of the methodology for endothelial cell counts.

Remember that these cells -- we are only counting 80 to 100 cells in most of these eyes, mean 109 even with selected images. If you are off by two or three cells, it makes a big difference in the calculated endothelial cell density.

With regard to the labeling, I would just like to make a suggestion and that is that we produce a graph something like this showing a calculated endothelial cell loss over time and relating the endothelial cell density to the age with endothelial cell density on the vertical axis and age on the horizontal axis using our best data available with the best projects of time so that I as a consumer, as an ethical physician, can have this information knowing that it would be best to implant or not implant depending upon these parameters. Thank you.

DR. WEISS: Thank you. We're going to go

on with the primary panel reviews. Dr. Mathers.

DR. MATHERS: Thank you, Dr. Weiss. Bill Mathers. I will relate to you my primary review. The application concerns a lens that is designed to correct myopia, moderate to high degree, five to 20 diopters by means of a lens device that is inserted into the anterior chamber and clipped to the anterior surface of the iris which maintains it's fixation and it's centration.

The highly myopic population has significant problems with spectacle correction. Contact lens are usually the preferred method of correction for this group if they are tolerated. Subject with dry eyes, surface disease, and other difficulties that preclude contact lens wear have few options.

We are given the question for the panel discussion, "Do the endothelial cell data presented in the overall analysis stratified by anterior chamber depth and extrapolated over time provide reasonable assurance of safety for the ARTISAN myopic lens?"

There are several safety considerations

that need to be addressed. The primary and overriding issue, however, is, I believe, the question of endothelial cell loss over time and the change in endothelial cell density resulting from the insertion and retention of the lens.

Data supplied by the applicant is presented in two forms, for the whole group and for smaller subgroups stratified by anterior chamber depth. For the whole group the endothelial loss rate for three years, the duration of the study was 4.75 percent and this is a loss rate of 1.58 percent per year with an N of 111. I realize my numbers are not exactly the same as some others that we've heard but I believe actually they have come up pretty close.

This contrast with the loss rate in the normal population of .6 percent and a loss rate of 2.5 percent for 10 years following cataract surgery. This cumulative endothelial loss is highly relevant to the younger population for which this lens is primarily intended. The table below indicates the resulting endothelial cell counts that could be expected if the loss continues at this rate for 10, 20, 30, or 40

years. I realize you may not have that in front of you but I'm going to go over the numbers.

Starting with 2,754 cells per square millimeter the mean endothelial cell density may seem reasonable but half the group will have an ECD less than this. The applicant has requested permission to use the device in 21-year-old subjects with an ECD down to 2,000. The main corneal clarity usually requires -- to maintain corneal clarity usually requires an ECD of 800. These are rough figures but they are probably correct.

For a reasonable margin of safety an ECD of 1,200 would be a better cutoff and even this is fairly low. Starting from the mean ECD and the lowest cell loss rate the average subject would be at risk after 40 years. Subjects with an initial ECD of 2,400, usually considered to be quite good cell count, would reach the point of risk at about 30 years.

If the subject had an ECD at the low end of 2,000, the 1,200 end point would be obtained in 23 years and the 800 ECD would be reached before 40 years. A cell count of 1,200 does not guarantee

imminent corneal failure but there is definitely an increased risk at this point. One needs to consider that these patients at that time are going to be facing cataract surgery which always has some consequence for the endothelium.

The data actually shows that the estimated loss rate from six months to three years, which is a total of 30 months, if this data is correct, then the loss rate is more like 1.9 percent per year. The resulting calculations shown above indicate that even starting with relatively high ECD of 2,754 the final ECD reaches 1,200 prior to 30 years. By 40 years the endothelial cell count is so low as to guarantee failure.

These calculations are based on a mean loss rate. Also given our 95 percent confidence internal which have a high-end loss rate of 6.1 percent for three years, or 2.03 percent per year. At this rate the 1,200 ECD is reached in about 26 years starting from the high end of 2,754.

Five percent may fall beyond this range and an ECD of 1,200 reached sooner than that.

Starting from an ECD of 2,000, which they are requesting, the 800 level is reached before 30 years. I want to point out here from today's discussion that Dr. Gray's assessment at 38 percent of the population could be expected to have a loss rate of two percent which is a failure rate, or 1,200 rate at only 25 years.

The highest loss rate was found in a group with an anterior chamber depth of 3 to 3.2. For this group the loss over three years, or maybe 30 months, I'm not sure, was 9.16 percent or 3 percent per year. This is a loss rate that is approximately double the group as a whole. Thus, the time to reach 1,200 or 800 is half the original calculation.

From an ECD of 2,000 less than 20 years would be required to reach 800. These calculations assume that the endothelial loss is close to the mean. Unfortunately, this is not likely to be the case since the standard deviation reported in the revised application is nearly twice the mean number. This indicates that some subjects will likely experience a substantially more rapid decline in their endothelial

cell density than these calculations show.

This device is currently marketed in over 40 countries and the report states that the device has not been removed from any of these for any safety concerns. This is not surprising because the time to achieve is sufficiently low ECD that would create corneal edema is still always over 15 years. Our 10-year data given to us before and also reanalyzed today I would think does not contraindicate or contradict this conclusion.

The endothelial cell losses are mostly less than those that have been reported for cataract surgery. A comparison with cataract surgery is relevant since clear lens extraction is one alternative that some practitioners use to correct extreme myopia.

For both operations there is a small incision into the anterior chamber and the device is implanted. Surgical trauma and postoperative inflammation could be expected to be of a similar range.

Cataract surgery is extremely common and

the risks are generally considered to be low and reasonable. Why is this different here? The age of the cataract surgery population is higher and, thus, the postoperative duration is much longer for the ARTISAN myopic lens.

In addition, preoperative vision loss is greater for the cataract group and the relative risk of surgery can be correspondingly greater. Finally, there are alternatives to phakic lens implants, whereas a cataract patient requires the replacement of the lens to restore vision in this new alternative.

Other safety concerns of shorter duration, less than 5 percent of subjects lost two lines of best corrected vision and 100 percent at three years had a best corrected of 20/40 or better within 228. This is in the range of cataract surgery where severe vision loss can be expected in the 1,000 to 2,000 or less range.

One subject was developing PSE cataract and we heard some other issues about cataract formation today that I'm not quoting. There was one case of a macular hole. Over time the incidence of

cataract may be higher because of subclinical inflammation from the lens.

But the rate of cataract development in this group is already higher than average and it will very difficult to make this attribution accurately. Postoperative inflammation in the form of cell and flare is persistent in 1.3 percent of subjects at six months.

This chronic inflammation may contribute to the cataract formation later. Corneal edema was surprisingly prevalent at 20 percent on day one and this dropped 2.2 percent in two weeks but I think this level is acceptable.

Regarding accuracy issues, the accuracy of the implant appears to be excellent considering the very great difficulties in determining chamber depth and refractive error and high myopes. Cataract surgery shows us that this can be actually quite hazardous to predict accurately.

Manifest refraction spherical equivalents were very good as 71.7 percent to 76 percent had an MRSE within .5 diopters of the target after six months

and 93 percent had within target with 1 diopter at six months.

The majority of subjects gained at least one line of best corrected vision which is quite remarkable. Visual side effects, glare and halos could be expected to occur if light passes outside the limits of the lens and enters the eye through the large pupil. This should occur primarily at night when the pupil is largest.

Such issues are real but of lesser concern since many of the subjects already experienced such visual symptoms without the lens in place. Severe glare was noted at one percent at all post-op visits. Halos were more common and were moderately severe in 17 percent and severe in 3.5 percent.

Regarding the assessment and recommendations, question 1 and 2, it is my opinion that the lens is not safe for the currently intended subject population. Endothelial cell loss is a progressive problem. The damage from ongoing cell loss could be partially ameliorated by requiring the pre-op cell count of greater than 2,400, or perhaps

some other number.

This would not completely solve the problem but it would help. It would also help to limit the age of the subjects. Those between 21 and 50 have different needs and issues compared with the older group.

It would be wise to be the most stringent with the younger group. The reviewer believes this lens is not safe to implant in subjects under the age of 35 regardless of the cell count. For those between 35 and 50 a cell count of at least 2,400 should be required. This would delay onset of the mean risk point, an ECD of 800 to age 75. Keeping in mind the wide 95 percent competence interval and the large standard deviations revealed in the data, this seems a reasonable level of risk.

As an alternative or additional method to reduce risk, the reviewer recommends the panel consider limiting the lens to those most in need, the group with a refraction of 9 diopters or greater. For this subset the alternatives are very limited and the added risk of late complications may be more

reasonable.

For subjects over the age of 50 the late complications, 30 and 40 years away, are less threatening even though there was a real probability that they will live -- these subjects will live into their 90s. For this group a pre-op ECD of 2,000 will still probably lead to failure in 30 years. This is, nevertheless, a reasonable risk that is in line with clear lens extraction or with early cataract removal, two likely alternatives.

There seems to be a very compelling reason to limit the lens to those with an anterior chamber depth greater than 3.2. For an anterior chamber depth less than this, endothelial cell loss was twice as high and clearly unacceptable at any age or ECD. I believe it is reasonable that the lens diameter should be limited to the size of the dark-adapted pupil, although I understand that the correlation of halos and glare is not very good and has some other considerations.

That concludes my remarks. Thank you.

DR. WEISS: Thank you, Dr. Mathers.

Dr. Schein.

DR. SCHEIN: If I can make this work, I'm just going to present an overview of the comments that I submitted several weeks ago. I'll try to move quickly through anything that's been pretty well covered already. I'm purposely not going to address the individual questions at the end but to make some more general comments that I had in reviewing the protocol.

I had some frustrations in reviewing it because I felt that the work was all there but I couldn't quite extract it in the way that I needed to in order to make the assessments regarding safety that I was trying to.

First let me make a few general comments. I believe there is consensus that some follow-up of reasonable length is needed to determine safety. In the cohort I examined, we only have three-year data on about a third of eyes. It makes it hard to think of complications rates after that distance. It's greater at two years, I understand, but perhaps only about 60 percent at that time. I'm not going to get into

protocol violations since we discussed that a lot this morning.

There has been a repeated theme which I would like to emphasize. When we're looking at safety, I would like to know safety not in some subgroup of patients, this Group A. I would like to know safety across the entire cohort that underwent the implantation of the device.

Obviously it would not report efficacy in a group, particularly efficacy related to corrected acuity in individuals who didn't meet a standardized entry acuity level but I do want to know this for adverse events.

There were, for example, about 50 eyes which were excluded from that primary analysis of Group A who appeared to have about twice the adverse event rate as defined by the sponsor. Likewise, I would like to look at safety issues or complication rates that in some way reflect the duration of time in the study.

For subjects that are lost to follow-up, there was a table which I've referenced there where

about 20 percent of them have some worrying anatomical or functional feature noted on the last exam recorded. Of course, these are patients that are excluded from the two or three-year rates of complications.

Another issue is I would like to see adverse events and safety talked about presented not just on a per-eye basis but on a patient basis. Certainly a patient who has a retinal detachment on one eye would view the procedure as risky even in the presence of one eye that didn't have such a problem.

The intent of this device is as a bilateral device and ultimately it will be used almost exclusively as a bilateral treatment much as contact lenses are used. So similarly at different places in the report there are different rates that were given. A quoted a rate of 3.4 percent, again, is not on a person level. It's on an eye level.

It's not accounting for variable length of follow-up so in these three year cumulative rates where a denominator of 662 is quoted, I don't know how to -- I don't know what inference to draw from that when I have less than one-half the potential data at

three years in hand.

There are references throughout the PMA and in the proposed labeling for comparisons with anterior chamber intraocular lenses. I think there may be historical reasons why these are in the document but I think they are inappropriate comparisons since patients undergoing anterior chamber intraocular lens are typically older. They are often already aphakic or they are in the process of suffering complications from cataract surgery, not a good comparison to make.

Looking at the safety issues, again, trying to figure out what the rates were, I had more difficulty trying to understand the differences between what were termed complications and/or adverse events. Lens opacity was listed as a complication but not cataract extraction. That seemed to be listed under other procedures. I found a couple under lens exchange.

The resuturing of a wound leak in the early postoperative period was called a secondary procedure. In my cataract practice I would call that

a complication. It's not the same as a secondary refractive procedure downstream to make more accurate the efficacy of the procedure. So there's inconsistency. Retinal detachment is a complication not listed as a secondary procedure. Again, all presented on a per-eye basis alone.

I would propose that complications be divided in analyses into those which have clinical significance with an obvious potential to cause harm and I've labeled a few of them here. There are others. And to distinguish those from I would call more trivial events such as the need for punctual occlusion or the need to widen a peripheral iridotomy.

The labeling of activities like needed to resuture or reposition an intraocular lens as a nonadverse event makes no sense to me clinically. Again, frustrating in trying to figure out what the true rates of adverse events actually was. Let's try to separate the things of clinical importance from those which are not.

Similar, this issue of something parsing events that might be potentially avoidable versus not.

I have even more trouble since I see no way to divorce the device itself from the surgical procedure that accompanies it. The material is polymethymethacrylate and is fine and inert. It has a wonderful track record but you cannot separate the two of them.

There is a presumption that the device and retinal detachment or, for that matter, development of cataract may be unrelated and that these are high myopes who are going to get these complications anyway. In the absence of a control group I think the sponsor takes the risk of a presumption of exactly the opposite.

The enrolled cohort here appropriately could not have had retinal detachment in the eye that was being enrolled either in the past year or in the past decade except for patients that were 30, 40, and 50 years old. By definition having not had them even though they were at risk, this is a group that is in a sense a survivorship group whose anticipated rate of such adverse events over a one, two, or three-year period would be expected to be lower, not higher.

So lens opacities, I believe, were recorded in about five percent of eyes but in the absence of a standardized grading system. I think someone made the implication earlier that in 1997 there was no concern about an aphakic intraocular lens in development of cataract and no understanding that endothelial cell counts were problematic and required multiple testing, repeat testing no matter what the name of the device was. I reject both of those notions. These things were well known in 1997.

It's difficult to assess. I don't know whether it's five percent or one percent or 10 percent. I am more concerned actually with the time dependent rate of cataract development than I currently am with projections three decades down stream for endothelial cell loss because as these patients age, they are likely to develop cataract, particularly if there is a risk of this device.

Such patients will have difficulties measuring the intraocular lens to replace and these patients will undergo cataract surgery combined with an anterior chamber lens removal which will certainly

add to the risk of cataract surgery.

Regarding patient-reported visual side effects depending on one's perspective you could look at this either as an efficacy or a safety issue. In looking at it from the safety perspective, I focus on individuals who do not report the symptom before surgery and then develop it later.

It's very nice that there are individuals who report it before who do not have it later. Again, from a safety public health perspective this is the group I'm most interested in and 15 to 30 percent developed symptoms of varying severity, usually not too severe but were ones that were not noted preoperatively.

This is something that I think can benefit from further analyses to see whether there were subgroups, age, gender, degree of refractive error, the obvious kinds of parameters to see if there are subgroups with really, really large rates that would be part of a patient education or even a labeling issue.

Finally, endothelial cell counts were left

unfortunately with having to draw inferences from data sets each one of which, I think, has substantial problems and limitations. Unfortunately, each data set does not compliment the other, at least in a meaningful way that I can see.

I'm actually drawn most towards the full data set. Although the image quality is poor, there is no reason to think there is a systematic bias towards under or over reporting. About 25 percent of individuals seem to have lost 10 percent or more cells which was substantially more than the proportion gaining 10 percent or more cells. I can't recall.

I think it was in the range of three to five percent that gained. So if it were purely noise, I would expect an equal distribution. Again, I couldn't tell from my own review how individuals who had secondary procedures or problems were handled or whether they were included or excluded.

This we've discussed further. Reanalyzing data reduces the individual variability but, as Dr. Stulting just point out, the measurements are still problematic because of test, retest or interpretation

and reinterpretation variability.

So we are left with non-US data. The Canadian data is means only and I feel very strongly that looking at means is not the way to look at endothelial cell count again. From a safety perspective we're interested in the worse X percent. We can argue whether it's five or 10 or 15 percent or 20 percent or more cell loss but it's that part of the distribution that you're worried about from the safety perspective.

European data has all the problems that we've already discussed. A third of the patients had lost 20 percent or more cells by 10 years but, again, I don't know how much faith to put in such a small sample. I think it would be worth some discussion to get some consensus on how much of incremental loss would be of clinical significance.

We've talked about 1,200 being a floor but I reject having a rigid final cutoff because of the anticipation that a large number of these patients are likely to undergo cataract surgery and lose another five to 25 percent based on that last intervention.

To summarize, I have concerns based on the data that's presented to date that is incomplete in comparison to what will presumably be collected over the next 18 months. Additional analyses of the kinds I've recommended and the three-year data, in other words, without any new data collection on patients that haven't been recruited, I think, would go a long way.

Particularly to these nonendothelial cell count issues one would be able to see whether the rates of retinal detachment and cataract surgery, lens reposition opacities was actually on the increase or whether there were things that tended to occur early and then flattened out. That would be very important to know. Thank you.

DR. WEISS: Thank. Dr. Macsai.

DR. MACSAI: Before I start, I would like to acknowledge -- I would like to thank the Agency for this opportunity to review this PMA. I would like to acknowledge the sponsor's work in putting it together and the extraordinary analysis by Drs. Lepri, Gray and Calogero.

In addition, I would like to echo some of Dr. Schein's sentiments. This was a very difficult PMA to analyze. It was difficult for a number of reasons but they mostly have to do with lack of standardization and probably protocol design.

As I said earlier, I think that we need to look at this in light of what we know about anterior chamber IOLs and what are the risks of phakic IOLs wherever they reside within the eye.

I submitted to the panel and to the Agency a long primary review which I know the sponsors received so what I would like to do is just highlight a few issues that I think warrant our review. The first is that of accountability. I felt the accountability of this PMA was moderate.

It dropped below 75 percent at the three-year exam. Dr. Stulting did tell us patients were only told they would need to be enrolled for two years. But what is of concern is that 53 percent of the subjects in this study are ongoing and perhaps we are looking at an incomplete data set.

Eleven percent were discontinued and of

these that were discontinued we learned earlier some were lost to follow-up and others had problems with the device. Those that had problems with the device are inappropriately grouped as discontinued. They should be listed as complications or treatment failures.

Enrollment. Of the 684 subjects 184 subjects were enrolled with protocol deviations in one or both eyes. This was discussed and apparently the Agency cleared these but, in my opinion, this is an alarming number of patients with protocol deviations. If the protocol is set up by the sponsors, perhaps they were too rigid in their initial establishment of enrollment criteria.

If you look at it this way, 25 percent of the subjects do not meet the enrollment criteria and this is making it even more difficult for us to analyze both the safety and efficacy of this device. When we look at criteria for safety and efficacy to quote, "The rates of cumulative and persistent complications should not exceed those of the FDA grid for anterior chamber IOLs."

I know this has been mentioned before but I have to go on record as saying this is not acceptable to me. The safety criteria for a phakic IOL should not be compared to that used during cataract surgery for an anterior chamber intraocular lens. In 2004, 1998, 1990 you used an anterior chamber IOL because things had gone wrong, disastrously wrong during cataract surgery.

In those patients an anterior chamber IOL was a second choice. Why would we compare an elective procedure that's refractive to an acceptable grid for a second choice in the treatment of a pathologic condition? The phakic IOLs must be held to a much higher standard than that of the FDA grid for ACIOLs.

If it is acceptable to some to make this comparison, then we have to look at the historical perspective of what has happened with ACIOLs in the United States and what has happened with numerous ACIOL designs, their effects on endothelial cells, the fact that most of the cornea surgeons at this panel meeting cut their teeth doing transplants and removing these anterior chamber IOLs.

We knew long ago about the risks of endothelial damage with the anterior chamber IOLs. If we are going to set this PMA up as comparable to the FDA grid for ACIOLs, then I think we should also be very careful about saying that we in 1997 did not necessarily have knowledge of endothelial cell standardization or damage, etc.

Dr. Stulting has gratefully produced some information about Group E which is the eyes not included in Groups A and B in which this was used compassionate use or custom made lenses or eyes that did not have a best corrected vision of 20/40. This data really needs to be reported to the implanting surgeon and the consumers.

It's a very, very important safety criteria. It's critical to know what happens when this lens is placed, for example, under a transplant or if it's a custom designed implants. The consumer must have this information and the information needs to be segregated based on the power of the IOLs, the age of the patients, the reason that the patients are in Group E.

Lens opacities. Twenty-six of the eyes had preoperative lens opacities. I said this at the beginning, they were not measured in any standardized manner. If you can't measure them standardized preoperatively, you can't measure them postoperatively and I think a comparison is ludicrous.

You're comparing apples to oranges. What's my opinion is different than your opinion as far as cataract formation in a lens. This is not able to be scientifically evaluated with this lack of standardization.

What about the safety of all lens powers? Well, only three implants were placed under 7 diopters. This is a very small end allowing for absolutely no statistical significance. What about the role of corneal abnormalities? It was very hard for me to figure out from this PMA what was defined as a corneal abnormality.

Was it Fuch's dystrophy or was it a little foreign body scar from contact lens wear? I don't know. Without that knowledge I can't tell if there is a skew in the endothelial cell count data that may

result from including these 41 eyes.

Adverse events. The sponsor stated that they thought an adverse event of one percent was acceptable and here I will echo the comments of Dr. Schein. You cannot arbitrarily decide what an adverse event is. Anything that happens as a result of the procedure that's bad is an adverse event.

If you look at these numbers of retinal detachment, cataract lens haptic dislocation, power calculation errors, inflammatory response, lenses explanted, lenses exchanged, lenses reattachment and surgical trauma, the numbers are much higher.

It's about a 3.9 percent incidence and I think that's per eye. I'm not sure if it's per patient. I really couldn't tell from looking at the data and I think it's really important to the consumer that they know the difference there because if they see it's per eye and they have two eyes, they may say, "Gee, is it twice that," whether we know or not the statistical validity of that assumption.

Patient symptoms. Again, it's very nice that they segregated out for us those patients who

preoperatively responded no and postoperatively responded yes. This removes the confounding variables of glare problems that we know are prevalent in this highly myopic population. It is very significant that in patients with pupils over 5.5 mm under mesopic conditions halos were reported in 23.8 percent. These are very high numbers.

These are very high numbers because the sponsor took the time to segregate out the pre-op response being no and the post-op response being yes. In many studies this has not been done so this is basically induced problems either from the procedure or the device or the surgical technique but they are induced problems.

Pressure. I have to defer to Dr. Coleman. I'm not a glaucoma specialist. Unfortunately I'm not good at even maybe defining it as Dr. Stulting alluded to those of us who are cornea surgeons, but I was very alarmed that gonioscopy was not performed in any of these patients preoperatively or postoperatively.

I am very concerned that in the darkly pigmented patient the role of pigment dispersion from

this lens may be very high. We just don't know yet but I find it hard to imagine that enclavation of the iris would not result in pigment release, flare, some level of chronic inflammation, and possible acceleration of cataract formation or glaucoma.

The endothelial cell data was very difficult to analyze. It's been adequately, I think, addressed by Dr. Gray, Dr. Mathers, and Dr. Schein. I have very little new to add. You all know that from baseline to three years the decrease was 4.7 percent but this loss seemed to be higher between the second and third year as compared to between the first and second year intimating that there is an increase in endothelial cell loss over time taking into account the lack of standardization of what we're looking at.

Anterior chamber depth was addressed by Dr. Mathers. There were only six eyes but in those eyes there was an alarmingly high rate of loss of endothelial cells alluding to the fact that the depth of the anterior chamber plays a big role in endothelial cell loss in these patients either from surgical trauma or ongoing trauma from eye rubbing or

something of that sort.

The number of eyes that demonstrated greater than 10 percent loss was analyzed and it was looked at. I don't need to go on about this. And a consistent cohort was also looked at showing 2.38 percent overall loss. Just clearly the endothelial cell count has not stabilized in this short time period that we're looking at during this accelerated review.

I don't know what the endothelial cell loss rate is but it's somewhere between 1.58 and 3 percent. I think that 2,000 cells per millimeter-squared is way too low of a cutoff, especially in a 21-year-old.

In summary I'll tell you that I had a very hard time reviewing this PMA due to lack of standardization and enrollment criteria, outcomes reporting, lens characterization, adverse event definition, gonioscopy, and specular microscopy. And though I'm not sure, I've chosen purposely not to answer the panel's questions during this presentation.

I would use this time to ask the Agency

and sponsors who are in the development process of improving our field by creating these phakic IOLs that it's very difficult to give a fair and reasonable analysis of safety and efficacy without standardization of these key features. Thank you.

DR. WEISS: Thank you very much. I want to thank all of the reviewers for their excellent and clear presentations. At this point we are going to go on to the panel discussion of this PMA. I would ask FDA if they could come forward to the podium and then just present each question so that we can discuss it in order.

While Dr. Lepri is doing that, the first question which I will just read out is, "Do the endothelial cell data presented in the overall analysis stratified by anterior chamber depth and the extrapolations over time provide reasonable assurance of safety in the ARTISAN myopia lens."

What I would like to do is just go around and get the opinions. If you want to give me a yes or a no, that's the best opinion possible. If you want to add some comments, that's okay as well.

Dr. Schein, do you think that there is reasonable assurance of safety on the basis of the endothelial cell data, question No. 1?

DR. SCHEIN: No.

DR. WEISS: Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: No.

DR. WEISS: Dr. McMahon.

DR. McMAHON: No.

DR. WEISS: Dr. Bradley.

DR. BRADLEY: I think it's impossible to project out 30 years. My answer is I don't know.

DR. WEISS: I don't know. Okay. Dr. Macsai.

DR. MACSAI: From the analysis of what I was given to review, I would have to say no.

DR. WEISS: Dr. Grimmett.

DR. GRIMMETT: In short, no.

DR. WEISS: Dr. Mathers.

DR. MATHERS: No, but I do think that the age of the patient when this is performed plays a role in that decision.

DR. WEISS: Dr. Casey.

DR. CASEY: No.

DR. WEISS: Dr. Coleman.

DR. COLEMAN: No.

DR. WEISS: Dr. Van Meter.

DR. VAN METER: No. This may not be the time to discuss it but I think that it's reasonable to talk about whether or not we want to lump all surgical and operative issues in with the device itself because we ourselves have said that anterior chamber lenses for pseudophakic correction are not a legitimate comparison because of the differences in surgical technique. These are sick eyes and they've had previous surgeons.

DR. WEISS: Actually, since we're not -- I just want to speak to the particular question so that may --

DR. VAN METER: No.

DR. WEISS: Dr. Smith.

DR. SMITH: No.

DR. WEISS: Dr. Huang.

DR. HUANG: I don't know.

DR. WEISS: Is there anyone that requires

any discussion on this point? I say this with great hesitancy. Is there anyone who just requires some discussion? Personally I think many of the points, if not all the points that are relevant, have already been elucidated. Okay.

Dr. Lepri, do you need anymore information from the panel on Question No. 1?

DR. LEPRI: I would say no. That was pretty clear cut to me.

DR. WEISS: We're trying. Question No. 2. I think this way of going around the table does work so we're going to try this another time. Question No. 2. "Do the other data, not the endothelial cell data but everything else, presented in the PMA provide reasonable assurance of safety?"

Dr. Schein.

DR. SCHEIN: No.

DR. WEISS: Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: No, and I would just like to second Dr. Schein's concerns about having to take into account time under observation for incidence of events.

DR. WEISS: Actually, from my elucidation, I would -- you can contradict me if you like. Would it be helpful to you if whoever -- if someone feels that the other data do not provide reasonable assurance safety, if they just specify what data they are concerned about?

DR. LEPRI: Exactly. I was just going to mention that to you. If you specify what in particular made you make that decision, it would be helpful to us.

DR. WEISS: So, Dr. Schein, you felt the other data do not provide reasonable assurance of safety. Can you just elucidate what your particular concerns are?

DR. SCHEIN: Lens opacities, retinal detachment. Need to move, reposition, or exchange the implant.

DR. WEISS: Are you concerned that there's a higher rate of retinal detachment with this lens than the normal patient?

DR. SCHEIN: The concern is that the procedure coupled with the device adds significant

risk of retinal detachment compared to not having the procedure or device.

DR. WEISS: Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: Yes. I would rely on the clinical expertise to specify where there's a concern. Then I just felt like the incidence rates that we've been given are probably undercut because they are not presented in a Kaplan-Meier or taking into account time under observation.

DR. WEISS: So you had safety concerns because the statistics as they were presented didn't give you the information you wanted?

DR. BANDEEN-ROCHE: Yes, in combination with the clinical concerns expressed by my colleagues.

DR. WEISS: Okay. Dr. McMahon.

DR. McMAHON: In the aggregate, no. If you look at the complication or adverse event rate as compiled by Dr. Schein and Dr. Macsai, the incidence rate is too high. If you start talking about individual rates, I have a hard time getting a handle around it to know whether that is too high individually or not.

DR. WEISS: So, from what I understand that you're saying, it's hard to answer this question because you don't have the numbers that you want.

DR. McMAHON: Correct.

DR. WEISS: What numbers would you want from sponsor? What would you like to look at which would allow you to make that determination?

DR. McMAHON: I think the time dependent issues that have already been raised are the ones that I would be looking for.

DR. WEISS: Dr. Schein.

DR. SCHEIN: And the parsing of events and complications from those with clinical significance separated from those without.

DR. WEISS: So basically put all the adverse events together and also put them in a format so that it's per patient and not per eye.

DR. SCHEIN: Or both.

DR. WEISS: Both. Anything else in terms of the statistical? Any other things that I have not mentioned that you would want?

DR. SCHEIN: No. I think Dr. Bandeen-

Roche emphasized we want the amount of time or timeline.

DR. WEISS: We want a timeline. We want binocular. We want monocular.

If you could just speak into the microphone so we can hear. Could you just repeat that so we can make sure we got it on the transcript.

DR. SCHEIN: I don't know how far back to rewind.

DR. WEISS: Tell us your wish list.

DR. SCHEIN: Yes. I think most of it is in the presentation I gave a few moments ago but it's to look at adverse events as a group on an eye and patient basis, adverse event being defined as occurrences which have the potential to cause significant harm or loss of vision and have those separated from adverse events such as the need for punctual occlusion, for example, which I do not feel have major clinical significance to present each of them on a per-eye and per-patient basis, and in a time dependent fashion so that we can see whether the likelihood of these complications, either individually

or cumulatively, is increasing with time or decreasing.

/ DR. WEISS: This is more of a data question as opposed to being convinced that aside from endothelial cell data that there is a higher -- there is no assurance of safety. In other words, if we had the data right here and you looked at it, you might have the possibility of saying that it's safe excluding questions on the endothelial cell data.

DR. SCHEIN: If we analyses on the entire cohort with a high or low-loss to follow-up at perhaps a three-year period, and they, indeed, showed a gradual decrement or lessening in adverse event rates, I would feel a lot better.

DR. WEISS: Dr. McMahon, did you have anything else to add?

DR. McMAHON: No.

DR. WEISS: Dr. Bradley.

DR. BRADLEY: I'm not sure. I'm still listening.

DR. WEISS: Dr. Macsai.

DR. MACSAI: Well, I think Dr. Schein has

very nicely summarized the issues for safety. But I also -- maybe this is speaking to efficacy but since the sponsor put outcomes of vision as part of safety, I would like to see the data stratified by lens power. We only saw it for Group AB and I would like to see it for everyone else. I guess I would like to see everyone all together all the time, not all these groupings.

DR. WEISS: So what I'm continuing to hear from members of the panel, again, aside from endothelial cell data, is the need for reprocessing the data looking at another way more information in order to make a determination of whether it is safe or not.

DR. McMAHON: Marian, are you looking for preoperative MSRE or do you think there is something specific relative to the implantable lens? They are going to be linked but --

DR. MACSAI: I'm not sure but when we looked at the stratified data that we got the day before the package was sent out to the primary reviewers and if you use 50 percent of eyes targeted